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SPECIAL REPORT

Allogeneic and autologous transplantation for haematological diseases, solid tumours and immune disorders: definitions and current practice in Europe

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The Accreditation Subcommittee of the EBMT regularly publishes special reports on current practice of haemopoietic stem cell transplantation for haematological diseases, solid tumours and immune disorders in Europe. Major changes have occurred since the first report was published in 1996. Haemopoietic stem cell transplantation today includes grafting with allogeneic and autologous stem cells derived from bone marrow, peripheral blood and cord blood. With reduced intensity conditioning regimens in allogeneic transplantation, the age limit has increased, permitting the inclusion of older patients. New indications have emerged such as autoimmune disorders and AL amyloidosis for autologous, and solid tumours for allogeneic transplants. The introduction of alternative therapies has challenged well-established indications such as imatinib for chronic myeloid leukaemia. An updated report with revised tables and operating definitions is presented here.

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Introduction

This report is the fourth in a series of reports from the Accreditation Subcommittee of the EBMT classifying allogeneic and autologous haemopoietic stem cell transplant (HSCT) procedures according to prevailing clinical practice in Europe.[1–4] During the decade since the first report was published, major changes have occurred in clinical practice based on new scientific and technical developments. This includes the recognition of new indications but also changed indications for HSCT, on the basis of important nontransplant developments such as the introduction of imatinib for treatment of chronic myeloid leukaemia (CML). Previously recognised limitations due to high risks for transplant related mortality such as age and comorbidity has been modified due to the introduction of allogeneic HSCT using reduced intensity conditioning regimens. The increasing use of two alternative sources of progenitor cells for allogeneic transplants, that is peripheral blood stem cells and cord blood, is also discussed. The updated classifications are presented below (Tables 1 and 2). As in the previous reports, it is not our intention to give formal evidence-based document or to provide arguments in favour of or against the decision to offer a given patient a transplant in a particular clinical situation. Rather, we have attempted to summarise the opinions and practice of clinicians working in transplant centres in Europe in 2005.[1–4] The recommendations are on the basis of existing prospective clinical trials, EBMT registry data, and expert opinions, but not on a formal review of the literature as many potential indications are rare and never can be supported by evidence from an adequately powered, randomized, controlled trial. There-

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fore, some recommendations have been made based on the basis of analogy, inference and expertise. Each section of the recommendations has been discussed within the appropriate working party of the EBMT. Furthermore, it has been circulated for comments to the leading participants of the European Leukaemia Network packages and to representatives of the national transplant societies in Europe. It is outside the scope of this report to classify indications on the basis of use of a particular conditioning regimen (reduced intensity or standard) or a particular stem cell source (bone marrow, peripheral blood progenitor cells, or cord blood). There are too many factors in the individual patient's situation (age, comorbidities, the availability of a donor, characteristics of the disease) that will influence such choices to make it feasible to include these in the report. Allogeneic and autologous SCT have moved from experimental procedures to routine clinical practice. As thousands of patients survive for long term, issues of quality of life and late side effects are becoming increasingly important. In children, late effects, such as growth retardation, sterility, impairment of intellectual ability and secondary tumours, have an even larger impact than in adults. It is, therefore, important when recommendations are made to analyse as well the possible survival gain from a SCT and the risk for late complications and the quality of life.

Definitions

Haematopoietic stem cell transplant

HSCT refers to any procedure where haemopoietic stem cells of any donor type and any source are given to a recipient with the intention of repopulating and replacing the haemopoietic system in total or in part. Stem cells can be derived from bone marrow, peripheral blood or cord blood.

Table 1 Proposed classification of transplant procedures for adults – 2005: (a) leukaemias, (b) lymphomas, (c) other diseases

Disease	*Disease status*	*Allo*			*Auto*
		Sibling donor	*Well-matched unrelated/1 ag related*	*Mm unrelated/ >1 ag related*	
(*a*)					
AML	CR1 (low risk[a])	CO	D	GNR	CO
	CR1 (intermediate or high risk[a])	S	CO	D	S
	CR2	S	CO	D	S
	CR3, incipient relapse	S	CO	D	GNR
	M3 Molecular persistence	S	CO	GNR	GNR
	M3 Molecular CR2	S	CO	GNR	S
	Relapse or refractory	CO	D	GNR	GNR
ALL	CR1 (low risk[a])	D	GNR	GNR	D
	CR1 (high risk[a])	S	S	CO	D
	CR2, incipient relapse	S	S	CO	GNR
	Relapse or refractory	CO	GNR	GNR	GNR
CML	First chronic phase (CP)	S	S	GNR	D
	Accelerated phase or >first CP	S	S	CO	D
	Blast crisis	GNR	GNR	GNR	GNR
Myeloproliferative disorders		CO	CO	D	CO
Myelodysplastic syndrome	RA, RAEB	S	S	CO	CO
	RAEBt, sAML in CR1 or CR2	S	CO	CO	CO
	More advanced stages	S	CO	D	GNR
CLL	Poor risk disease	S	S	D	CO
(*b*)					
Aggressive B-cell NHL					
Diffuse large cell	CR1 (intermediate/high IPI at dx)	GNR	GNR	GNR	CO
	Chemosensitive relapse; ⩾CR2	D	D	GNR	S
	Refractory	D	D	GNR	GNR
Mantle cell lymphoma	CR1	D	D	GNR	S
	Chemosensitive relapse; ⩾CR2	D	D	GNR	S
	Refractory	D	D	GNR	GNR
Lymphoblastic lymphoma	CR1	D	GNR	GNR	CO
and Burkitt's lymphoma	Chemosensitive relapse; ⩾CR2	CO	D	GNR	S
	Refractory	D	D	GNR	GNR
Follicular B-cell NHL	CR1 (intermediate/high IPI at dx)	GNR	GNR	GNR	CO
	Chemosensitive relapse; ⩾CR2	CO	CO	GNR	S
	Refractory	D	D	GNR	D
T-cell NHL	CR1	D	GNR	GNR	CO
	Chemosensitive relapse; ⩾CR2	D	D	GNR	CO
	Refractory	D	D	GNR	GNR
Hodgkin lymphoma	CR1	GNR	GNR	GNR	GNR
	Chemosensitive relapse; ⩾CR2	D	D	D	S
	Refractory	D	D	GNR	CO

Table 1 Continued

Disease	*Disease status*	*Allo*			*Auto*
		Sibling donor	*Well-matched unrelated/1 ag related*	*Mm unrelated/ >1 ag related*	
(*c*)					
Myeloma		CO	D	GNR	S
Amyloidosis (AL)		CO	D	GNR	CO
Severe aplastic anaemia	Newly diagnosed	S	GNR	GNR	GNR
	Relapsed/refractory	S	S	CO	GNR
Paroxysmal nocturnal haemoglobinuria		S	CO	CO	GNR
Breast cancer	Adjuvant and inflammatory	GNR	GNR	GNR	D
Breast cancer	Metastatic responding	D	D	GNR	D
Germ cell tumours	Sensitive relapses	GNR	GNR	GNR	S
Germ cell tumours	Refractory	GNR	GNR	GNR	CO
Ovarian cancer	MRD	GNR	GNR	GNR	D
Ovarian cancer	Refractory	D	D	GNR	GNR
Glioma	Post-surgery	GNR	GNR	GNR	D
Small cell lung cancer	Limited/'good'; upfront	GNR	GNR	GNR	D
Renal cell carcinoma	Metastatic	D	D	GNR	GNR
Immune cytopenias		D	GNR	GNR	CO
Systemic sclerosis		D	GNR	GNR	CO
Rheumatoid arthritis		GNR	GNR	GNR	CO
Multiple sclerosis		D	GNR	GNR	CO
SLE		D	GNR	GNR	CO
Crohn's disease		GNR	GNR	GNR	CO
CIDP		GNR	GNR	GNR	D

S = standard of care, generally indicated in suitable patients; CO = clinical option, can be carried after careful assessment of risks and benefits; D = developmental, further trials are needed; GNR = Generally not recommended; CR1, 2, 3 = first, second, third complete remission; RA = refractory anaemia; RAEB = refractory anaemia with excess blasts; sAML = secondary acute myeloid leukaemia; IPI = International prognostic index; MRD = Minimal residual disease; CIDP = chronic inflammatory demyelinating polyradiculoneuropathy; SLE = systemic lupus erythromatosis.
This classification does not cover patients for whom a syngeneic donor is available; mm = mismatched.
[a]Categories are based mainly on number of white blood cells, cytogenetics at diagnosis, and time to achieve remission according to international trials.

For allogeneic transplants, repopulation can be measured by determining chimerism in the peripheral blood and/or bone marrow. The goal of the procedure should be defined beforehand and a documented informed consent of the patient (and donor) should be obtained before the procedure.

Donor categories

An HLA-identical sibling donor is defined as genotypically identical or phenotypically identical. A well-matched unrelated donor is defined as a 9/10 or 10/10 identical donor on the basis of a high-resolution typing. A mismatched unrelated donor is defined as a 6–8/10-matched donor on the basis of a high-resolution typing. A good collaboration with the HLA-typing laboratory is essential for the selection of the best available donor.

Donor lymphocyte infusions

Donor lymphocyte infusions (DLI) are defined as the infusion of lymphocytes (or subsets thereof), which are obtained from the previous donor of an allogeneic HSCT to enhance engraftment, shift the balance between the donor and recipient haemopoiesis in favour of donor type, prevent rejection or treat, or prevent, relapse. The goal of the procedure should be defined beforehand and a documented informed consent of the patient and donor should be obtained before the procedure.

Patient age

The age of an individual patient remains one of the most important determinants of outcome following both allogeneic and autologous HSCT-procedures. Generally, HSCT in children gives better results than in adults. Age cannot be seen as a single risk factor but must be taken together with other factors in the decision-making regarding HSCT. It should, however, be recognised that biological rather than chronological age is the more important determining factor for outcome. As in previous reports, patients up to the age of 16 years are, for the purpose of this document, classified as children.

Stem cell sources

Bone marrow (BMT) and G-CSF-mobilised peripheral blood progenitor cells (PBSCT) are standard sources of haematopoietic stem cells. For autologous HSCT, PBSCT has become the preferred choice owing to its more rapid haematopoietic reconstitution. For allogeneic HSCT, both sources are used. Both methods have their specific advantages and disadvantages. There are marked differences in side effects for the donors. Peripheral blood stem cells are associated with more rapid engraftment in the recipient. A major concern with allogeneic PBSCT is the increased incidence of chronic GVHD, compared to BMT. Although it has been shown in some studies that for patients with advanced disease, transplantation-related mortality and disease-free survival are better with allogeneic PBSCT than with allogeneic bone marrow trans-

Table 2 Proposed classification of transplant procedures for children – 2005. (a) haematological malignancies, (b) other disorders

Disease	*Disease status*	*Allo*			*Auto*
		Sibling donor	*Well-matched unrelated/1 ag related*	*Mm unrelated/ >1 ag related*	
(*a*)					
AML	CR1 (low risk)	GNR	GNR	GNR	GNR
	CR1 (high risk)	S	CO	GNR	S
	CR1 (very high risk)	S	S	CO	GNR
	CR2	S	S	S	S
	>CR2	CO	D	D	GNR
ALL	CR1 (low risk)	GNR	GNR	GNR	GNR
	CR1 (high risk)	S	CO	CO	GNR
	CR2	S	S	CO	CO
	>CR2	S	S	CO	CO
CML	Chronic phase	S	S	D	D
	Advanced phase	S	S	D	GNR
NHL	CR1 (low risk)	GNR	GNR	GNR	GNR
	CR1 (high risk)	CO	CO	GNR	CO
	CR2	S	S	CO	CO
Hodgkin's disease	CR1	GNR	GNR	GNR	GNR
	First relapse, CR2	CO	D	GNR	S
Myelodysplastic syndromes		S	S	D	GNR
(*b*)					
Primary immunodeficiencies		S	S	S	NA
Thalassaemia		S	CO	GNR	NA
Sickle cell disease (high risk)		S	CO	GNR	NA
Aplastic anaemia		S	S	CO	NA
Fanconi anaemia		S	S	CO	NA
Blackfan–Diamond anaemia		S	CO	GNR	NA
MPS-1 H Hurler		S	S	CO	NA
MPS-1 H Hurler Scheie (severe)		GNR	GNR	GNR	NA
MPS-VI Maroteaux-Lamy		CO	CO	CO	NA
Osteopetrosis		S	S	S	NA
Other storage diseases		GNR	GNR	GNR	GNR
Autoimmune diseases		GNR	GNR	GNR	CO
Germ cell tumour		GNR	GNR	GNR	CO
Ewing's sarcoma (high risk or >CR1)		D	GNR	GNR	S
Soft tissue sarcoma (high risk or >CR1		D	D	GNR	CO
Neuroblastoma (high risk)		CO	GNR	GNR	S
Neuroblastoma >CR1		CO	D	D	S
Wilms tumour >CR1		GNR	GNR	GNR	CO
Osteogenic sarcoma		GNR	GNR	GNR	D
Brain tumours		GNR	GNR	GNR	CO

S = standard of care, generally indicated in suitable patients; CO = clinical option, can be carried out after careful assessment of risks and benefits; D = developmental, further trials are needed; GNR = not recommended; NA = not applicable; CR1, 2 = first, second complete remission; mm = mismatched.
This classification does not cover patients for whom a syngeneic donor is available.

plantation (BMT), these results have not been confirmed in individuals transplanted with early disease. For selected situations such as high stem cell dose allografts from haploidentical donors, peripheral blood might be superior in adult patients. Preliminary results fail to show an advantage for PBSCT compared to bone marrow in severe aplastic anaemia, and a higher risk for chronic GVHD might even result in poorer survival. The higher risk for chronic GVHD might also make PBSCT a less attractive option for children.[5] The donor's preferred choice must be taken into account.

In general, cord blood stem cells may be used in the context of HLA genotypically identical allogeneic HSCT, but more frequently, it is used when patients do not have an HLA-identical or a HLA-matched peripheral blood or marrow donor, or the patient's condition requires prompt transplantation. Cord blood transplantation has emerged as an effective transplant modality, primarily in children as a minimum dose of 2×10^7 nucleated cells/kg at infusion is recommended. However, cord blood transplantation is also increasingly used in adult patients with promising results. HLA identity is preferable but disparity should not exceed two HLA-antigens. Cord blood units should be selected firstly according to nucleated cell dose or the number of CD34+ cells, and secondly according to the number of HLA mismatches. The indications for the use of cord blood as a source for stem cells in children are identical to the indications listed in Table 2. Cord blood can also be used in adults if the cell dose and HLA-matching requirements are met. The use of double cord blood transplantation and reduced intensity conditioning regimens using cord blood cells are under investigation.

Allogeneic transplants with reduced intensity conditioning regimen

Conditioning regimens vary in their intensity and can be classified as standard intensity conditioning, reduced intensity conditioning or intensified conditioning regimens. Reduced intensity conditioning regimens can be used in the allogeneic setting with the intention of shifting the balance between risk of transplantation-related mortality and risk of relapse. Allogeneic transplants with reduced intensity conditioning are increasingly used for the treatment of malignant and nonmalignant diseases. During the last years, approximately 25% of all allogeneic HSCT were performed with reduced conditioning regimens. Many different terms are used in the literature such as mini-transplants, microtransplants, nonmyeloablative conditioning regimens, etc. The preferred term should be 'reduced intensity conditioning' (RIC) HSCT. A wide variety of reduced intensity conditioning regimens have been described in publications and RIC HSCT shall preferably be performed with a previously published protocol to gain adequate experience with a few protocols. However, there is no general agreement on the definition. Extensive feasibility studies have been published and short-term results clearly show that RIC HSCT can decrease the risk for early transplant-related mortality, thereby making transplants for older patients and for patients with co-morbidities possible. The results of RIC HSCT after 1–3 years (intermediate-term) vary with disease and stage of disease but are encouraging enough to proceed forward. Molecular remissions with completed donor chimerism are holding now more than 5 years after transplantation.

In many patients, a RIC HSCT is the only curative treatment available. Results have been published in phase I studies for related donor HSCT up to 75 years and for unrelated donor HSCT up to 70 years. The preferred stem cell source has been peripheral blood (90%). Experience with unrelated donors has been published with results comparable to those with related donors. A conventional transplant remains the therapy of choice for younger patients without comorbidities in the absence of results from prospective, controlled trials. RIC transplants are discouraged in patients with progressive or refractory disease.

Haploidentical T-cell-depleted HSCT

The use of haploidentical donors for HSCT can be indicated when no other donor can be found and when an otherwise curative approach is not available. Haploidentical grafts should contain $>5.0\times10^6$ CD34 + cells/kg. For this purpose, developmental or pilot studies can be approved in specialised centres.

Categorisation of transplant procedures

Standard of care (S)

Transplants categorised as 'standard of care' can be carried out in many centres in Europe. The results of such transplants are reasonably well defined, and compare favourably (or, are superior to) results of nontransplant treatment approaches. Obviously, defining a transplant as the standard of care does not mean that it is necessarily the optimal therapy for a given patient in all clinical circumstances. 'Standard of care' transplants may be performed in any specialist centre with experience with HSCT procedures, provided they have an appropriate infrastructure as defined by the EBMT and JACIE guidelines.[6] Reporting of data to international transplant registries is strongly recommended, and mandatory for EBMT members.

Clinical option (CO)

This category was in the previous version of the report named 'clinical protocol'. The renaming to 'Clinical Option' is on the basis of the fact that the possibilities given by the present available transplant techniques and the importance of patient factors such as age and comorbidity makes the assessment of indications for transplantation much more complex. For example, the reduced early mortality achieved by reduced intensity conditioning regimens has changed the risk/benefit analyses of allogeneic HSCT compared to other available treatment options. It is also recognised that for many indications, the number of patients will be low and therefore data regarding the value of HSCT is difficult to assess. Our current interpretation of existing data for indications in this category supports that HSCT is a valuable option for individual patients after careful discussions of risks and benefits with the patient; but that for groups of patients, the value of HSCT for patients included in this category needs further evaluation. Furthermore, it is necessary to carefully weigh the available donor, the stem cell source, and the conditioning regimens used as outcome is likely to vary depending on these choices. Transplants for indications under this heading should be performed in a specialist centre with major experience with HSCT procedures, with an appropriate infrastructure as defined by EBMT guidelines and, optimally, shall meet JACIE standards.[6,7] Reporting of data to the international transplant registries, preferably so-called MED-B data, is strongly recommended to allow the further assessment of the value of HSCT in these indications. Reporting of MED-A data is mandatory for EBMT members.

Developmental (D)

Transplants have been classified as developmental if there is little experience with this particular type of transplant and when additional research is needed to define the role of HSCT. These transplants should be performed within the framework of a clinical protocol. Such a protocol can either be a randomised comparison of two or more approaches to treatment, or a small pilot series undertaken by transplant units with acknowledged expertise in the management of that particular disease or that type of HSCT. Patients are therefore offered the opportunity to undergo allogeneic or autologous HSCT in the context of a study that has been designed specifically to cover a series of patients who satisfy defined diagnostic criteria. The protocol may be performed in a single institution or may reflect national or international multicentre collaboration. The category also covers

fundamentally new approaches to the management of a disease that, in a different stage, may already be classified under the standard of care or clinical option. Protocols for 'developmental' transplants has to be approved by local research ethics committees and must be according to current international standards. It is implied that the results of the study are intended for presentation to and/or publication for the medical community at large. Centres performing transplants under the category of 'developmental' should meet JACIE standards.[5] The document for Rules and Regulations for EBMT Clinical Trials could also be used as a guideline (http://www.ebmt.org/1WhatisEBMT/Op_Manual/OPMAN16_Clinical%20Trials%20-Guidelines.pdf). The reporting of data to the international transplant registries, preferably so-called MED-B data, is strongly recommended to allow further assessment of the value of HSCT in these indications. Reporting of MED-A data is mandatory for EBMT members.

Generally not recommended

The generally not recommended (GNR) category includes early disease stages when results of conventional treatment do not normally justify the additional risk of transplantation-related mortality, or when the disease is so advanced that the chance of success is so small and that the risk of the harvest procedure for the normal donor is difficult to justify. 'GNR' may not apply to specific situations where a syngeneic donor exists.

This category includes HSCT for a disease in a phase or status in which patients are conventionally not treated by HSCT. Therefore, there will be some overlap between 'GNR' and 'D', and further research might be warranted within prospective clinical studies for some of these indications. 'GNR' does not exclude that centres with a focus on a certain disease can investigate HSCT in these situations. If a HSCT is performed on a 'GNR' indication, the reporting of MED-A data to the EBMT registry is mandatory for EBMT members and reporting of so-called MED-B data is strongly recommended to allow further assessment of the value of HSCT in these indications.

Status of transplants in specific diseases in adults

The updated classification of HSCT procedures in adults is shown in Table 1.

Acute myeloid leukaemia

Patients with acute myeloid leukaemia (AML) in first remission may be treated by allogeneic or autologous HSCT on an individual basis or within the context of a clinical study. Allogeneic HSCT for patients in first remission with cytogenetically 'favourable' subtypes (t(8;21); inv(16)); t(15;17) is not recommended. However, in patients with AML M3 with molecular PML/RARA persistence after consolidation or salvage treatment, an allogeneic transplant from an HLA-identical sibling is recommended or is an option from an HLA-matched unrelated donor. Patients in the first remission with other cytogenetic abnormalities or normal karyotype (including those with the presence of FLT-3 mutations) are candidates for HLA-identical sibling donor transplantation. Patients in first complete remission considered as high-risk owing to specific cytogenetic abnormalities are candidates for an allogeneic HSCT from either an HLA-identical sibling or unrelated donor. Patients who fail to achieve complete remission (CR) after one course of induction chemotherapy may be treated by allogeneic HSCT with an HLA-identical sibling, or if time permits, from an unrelated donor. Patients with refractory AML in an early relapse or in second or later remission may also be treated by allogeneic HSCT. Patients with AML in first remission may be treated by auto-HSCT with or without purging of the graft when an allogeneic donor is not available. The results of transplant procedures for AML must be compared with results of contemporary chemotherapy regimens. Recently, promising results have been reported with unrelated cord blood and T-cell-depleted haploidentical HSCT for patients with AML.

Acute lymphoblastic leukaemia

Patients with acute myeloid leukaemia (ALL) with poor prognostic features, for example t(9;22) or t(4;11), or delayed time to obtain remission are candidates for allogeneic HSCT from either an HLA-identical sibling or an unrelated donor. Allogeneic HSCT for standard risk patients in first CR should be performed within a clinical protocol. Patients who relapse after chemotherapy and achieve a second complete remission are candidates for allogeneic HSCT from an HLA-identical sibling or an unrelated donor.

Chronic myeloid leukaemia

HSCT remains the only curative treatment for chronic myeloid leukaemia (CML). Current data suggest that the following patients should be considered for HSCT in the first chronic phase: patients on imatinib therapy who do not achieve an haematological response within 3 months, absence of any cytogenetic response within 6 months, no complete cytogenetic response within 1 year, or patients who lose a molecular, cytogenetic or haematological response under imatinib therapy. The EBMT risk score (Gratwohl score) might be used to identify patients at low or high risk for transplant-related mortality and who therefore should be considered for a RIC HSCT; and might also be used in combination with the Sokal or Hasford score for identifying patients to undergo HSCT and has a low risk of transplant-related mortality, but an increased risk for disease progression without HSCT. Older patients and younger patients with concomitant diseases might be suitable for RIC HSCT. Patients with controlled accelerated phase and blast crisis might receive a conventional transplant. A patient with a syngeneic donor is always a candidate for a HSCT with standard conditioning. Autologous HSCT might decrease disease progression in patients with CML.

Myeloproliferative disorders other than CML

Allogeneic HSCT is today the only curative option for patients with myeloproliferative disorders. Although the experience with allogeneic HSCT in patients with PV, primary myelofibrosis and other myeloproliferative dis-

eases is limited, it is reasonable to consider patients with high-risk disease for allogeneic HSCT as a clinical option. Ideally, such patients should not have more than 10% of blasts. Autologous HSCT can induce responses in patients with primary myelofibrosis.

Myelodysplastic syndromes
Allogeneic HSCT is considered the treatment of choice for patients with myelodysplastic syndromes (MDS) or secondary AML, and offers a good chance of long-term disease-free survival, if the treatment is performed at an early stage of the disease, or if the patient is transplanted in CR after chemotherapy. The international prognostic score (IPSS) is a valuable tool to assess a patient's prognosis without transplantation. The results seem to be better in allogeneic HSCT if the blast count is not exceeding 10% at the time of transplant. Autologous HSCT is tested in clinical protocols in patients who achieve CR after chemotherapy.

Chronic lymphocytic leukaemia
Allogeneic stem cell transplantation is a possible treatment option for younger patients who have been previously treated and have poor-risk disease as defined by clinical and cytogenetic assessments. Mature phase-II studies and registry analyses have shown that allogeneic HSCT is the only therapy in chronic lymphocytic leukaemia (CLL) with proven curative potential. In contrast to conventional treatment, it can provide long-term disease control even in genetically unfavourable and refractory cases, and is clearly superior to any other salvage regimen despite an increased transplant-related mortality when used with standard conditioning. There is no evidence for inferiority of unrelated donor transplants. Thus, allogeneic HSCT may be offered to suitable patients as standard procedure. Autologous stem cell transplantation could be considered for patients with poor-risk disease in complete or good partial remission, able to withstand high-dose therapy. Autologous transplantation should be performed preferably in the context of a clinical protocol, such as the EBMT CLL auto-protocol.

Hodgkin's lymphoma
Autologous HSCT is the standard therapy for relapsed patients. There is no current indication for autologous HSCT in first CR even in patients with bad prognostic features at diagnosis. Moreover, the use of intensive first-line chemotherapies (e.g., BEACOPP, Stanford V) will reduce the percentage of primary refractory patients. Patients with disease refractory to firstline therapy but sensitive to salvage therapy might benefit from an autologous HSCT. For truly primary refractory patients or for patients in chemo-refractory relapse, autologous HSCT has only a small likelihood to induce a long-term remission, but might be considered as an initial debulking therapy in the context of tandem procedures followed by an allogeneic HSCT as consolidation therapy. Reduced-intensity conditioning protocols could be considered in most patients since the transplant-related mortality in the context of conventional allogeneic HSCT is very high. A conventional conditioning regimen should therefore only be considered for selected young patients.

Lymphocyte predominant nodular Hodgkin's lymphoma (HL) has to be considered a completely separate entity in terms of HSCT. For patients with lymphocyte predominant HL, an indication for HSCT rarely exists.

Non-Hodgkin's lymphoma
Patients with follicular non-Hodgkin's lymphoma (NHL) are normally not candidates for an autologous HSCT as first-line therapy although, some studies suggest a role for this procedure in some subgroups of high-risk patients. Autologous HSCT remains the standard approach for early relapsing patients. In late relapsing patients, the advantages are less clear. Patients relapsing after an autologous HSCT can be considered for an RIC allogeneic HSCT using an HLA-compatible sibling or unrelated donor.

The data of autologous HSCT in patients with transformed lymphoma suggest an improved prognosis if these patients have a good response to chemotherapy.

Autologous HSCT is considered a standard procedure for patients with relapsed aggressive B-cell NHL. The evidence supporting autologous HSCT as first-line therapy is less strong although, it can be considered as an option in patients with bad prognostic features at diagnosis. Patients relapsing after an autologous HSCT can also be considered candidates for an allogeneic HSCT using an RIC protocol with an HLA sibling donor or an unrelated donor. Autologous HSCT is not an option for refractory patients.

Patients with mantle cell lymphoma should be considered candidates for early intensification with an autologous HSCT, owing due to the inherent bad prognosis of the disease. A tandem approach with an auto-HSCT as debulking therapy followed by an allogeneic HSCT using a RIC protocol can be considered a developmental approach.

Patients with lymphoblastic lymphoma may be consolidated in remission by autologous HSCT. Allogeneic HSCT might be considered for young adults in first remission. Other high-risk NHL such as Burkitt's lymphoma could also benefit from autologous HSCT in first remission. The experience with allogeneic HSCT for Burkitt's lymphoma is still limited.

Indications and results of HSCT may change for the subgroup of CD20+ lymphomas due to the widespread use of rituximab.

T-cell NHL usually has a poor prognosis. The potential benefit of an early intensification with autologous HSCT should be studied by prospective clinical trials. Allogeneic HSCT using a RIC protocol can be considered as consolidation treatment after first-line therapy.

Myeloma
Autologous HSCT is clearly indicated for patients less than 70 years of age who respond to first-line treatment. Some nonresponding patients might also benefit from this approach. Furthermore, double autologous HSCT were superior to one autologous HSCT. However, the vast majority of patients still relapse. TBI should not be used in

the conditioning regimen owing to increased toxicity without appreciable benefit. Allogeneic HSCT is a treatment with curative potential, but is associated with considerable transplant-related mortality and might be used in selected high-risk patients. The combination of auto-HSCT followed by RIC HSCT has been studied in phase II studies. The results of a phase III study comparing double auto-HSCT with the combination of auto-HSCT followed by RIC HSCT in newly diagnosed myeloma patients up to age of 70 years will be available in late 2005 and no recommendation can therefore be given at present. The combination of auto-HSCT and unrelated RIC HSCT is currently being investigated and will be studied in a phase III protocol of the EBMT.

AL amyloidosis
Patients with AL amyloidosis have been treated by autologous HSCT. A study with matched controls showed that amyloidosis patients without severe heart failure benefited from high-dose therapy and auto-HSCT. Allogeneic HSCT might be considered as a clinical option in patients with progressive disease.

Acquired severe aplastic anaemia
Allogeneic BMT from an HLA-identical sibling is usually the treatment of choice in patients with severe aplastic anaemia (SAA) under the age of 30 years. The choice in patients between 30 and 45 years of age is more difficult and both BMT and immunosuppression give good results. In older patients, or in the absence of an HLA-matched sibling, an initial course of a combination of ATG and cyclosporine should be given. The median time for response after this treatment is 2–3 months. One should, therefore, wait at least 4 months for assessment of response before a transplant is undertaken, especially if from an unrelated donor. The conditioning regimen should not include irradiation because of the high risk of secondary tumours. Unrelated donor and mismatched family donor transplants are still associated with significant morbidity but can be undertaken as a clinical option when other therapies have failed.

Constitutional SAA, including Fanconi anaemia
Allogeneic HSCT is the only curative treatment for patients with constitutional SAA. For patients lacking an HLA-identical sibling donor, transplantation could be considered from an unrelated donor. The conditioning regimen should preferably not include radiation and the dosage of the chemotherapy reduced as appropriate for patients with Fanconi anaemia

Paroxysmal nocturnal haemoglobinuria
Small numbers of patients with paroxysmal nocturnal haemoglobinuria (PNH) have been treated with allogeneic HSCT, which seems to be the only curative approach. For patients with high-risk disease, who have an HLA-identical sibling, an allogeneic HSCT is a clinical option.

Solid tumours
The value of HSCT in solid tumours remains, despite large numbers of transplants performed, difficult to assess. On the basis of available data, autologous HSCT for certain groups of patients with neuroblastoma, Ewing sarcoma and extragonadal germ cell tumours can be accepted as 'clinical option'. Several large randomised trials for the autologous HSCT as therapy of adjuvant and metastatic high-dose chemotherapy (HDC) trials for breast cancer have failed to show a benefit of HSCT. A meta-analysis evaluating the efficacy of HDC in breast cancer is underway with participation of the EBMT. Therefore, auto-HSCT for breast cancer cannot be recommended either in the adjuvant or metastatic setting outside a clinical trial. There is also no prospective randomised trial showing the efficacy of HDC in patients with ovarian cancer, small-cell lung cancer and germ cell tumours. Therefore, autologous HSCT for solid tumours should be undertaken only as a part of approved clinical protocols and most such protocols should now be randomised.

The interest for allogeneic HSCT for solid tumours has increased with the introduction of RIC HSCT and after the first reports of CR achieved by allogeneic HSCT in some patients. New categories of solid tumours such as renal cell carcinoma have thereby become possible indications for allogeneic HSCT. Ongoing studies will have to define the place of allogeneic HSCT in these patients and currently all such transplants shall be performed in the framework of clinical research protocols.

Autoimmune disorders
Autologous HSCT following appropriate conditioning to maximize the immunosuppression is being considered in clinical protocols for selected patients with severe multiple sclerosis, rheumatoid arthritis, systemic lupus erythromatosis, systemic sclerosis, immune cytopenias and Crohn's disease. Autologous HSCT for other autoimmune disorders is being considered on a developmental basis. Dependency of high steroid doses above the 'Cushing threshold' and causing skeletal damage could be an indication. Allogeneic HSCT is being considered on a developmental basis in patients selected for very poor prognosis.

Status of transplants in specific diseases in children

Acute myeloid leukaemia
Allogeneic HSCT from an HLA-identical sibling represents an absolute indication for children defined as high risk. This has proved to be more efficient than chemotherapy alone in most comparative studies, with event-free survival (EFS) ranging from 55 to 72% in children, given the transplant in CR1. Autologous HSCT has been largely used as consolidation in children with AML, in CR1 after induction therapy and represents a valid alternative for high-risk children lacking a matched sibling donor. The use of peripheral blood progenitor cells in children with AML given autologous HSCT is not frequent, mainly because of the difficulties in collecting adequate numbers of circulating haematopoietic progenitors and the poorly defined effect in

this subset of children. Infant AML and children with FAB M0, M6 or M7 AML, who stand very poor chances of cure by chemotherapy or by autologous HSCT are indications for unrelated donor HSCT. Results in children with AML undergoing haploidentical HSCT have shown an effect of NK alloreactivity suggesting that the haploidentical option may have a role in early phase very high-risk AML patients.

Acute lymphoblastic leukaemia
Indications for HSCT in children with ALL in CR1 are limited to only those 8–10% who constitute a subpopulation of high-risk ALL. Most study groups define these patients as having estimated EFS of less than 50%. The risk factors indicating the usefulness of HSCT are known molecular biological markers or chromosomal abnormalities, and biological factors including poor prednisone response and resistance to initial chemotherapy.

ALL patients, who experience an early marrow relapse, still have a dismal prognosis when treated with conventional chemotherapy. Although nearly 90% achieve a CR2, most of them subsequently develop progressive disease. Both matched sibling donor HSCT and unrelated donor HSCT are clearly indicated in these patients. If a matched sibling or a well-matched unrelated donor cannot be identified, other types of donors such as cord blood, mismatched unrelated donors or haploidentical family donors might be indicated. The indication for autologous transplantation is limited to a small subset of patients with either a late bone marrow relapse or an extramedullary recurrence.

Chronic myeloid leukaemia
The results from HSCT with HLA-identical or unrelated donors performed within 6 months from diagnosis suggest that HSCT is indicated and needs to be planned early in the course of the disease. Unanswered questions surround the role of tyrosine kinase inhibitors such as imatinib, particularly for those children without an HLA-identical or well-matched donor. Prospective, randomised studies are needed to address this complex issue.

Malignant lymphoma
Children suffering from lymphomas have a good prognosis when treated with first line therapy such as chemo- and radiotherapy. Patients who fail to respond to this approach or with recurrent diseases can achieve long-term disease-free survival after autologous HSCT. The true impact of allogeneic HSCT in children with lymphomas has not been clarified. The high transplant-related toxicity after these transplants, due also to the advanced disease status of the patients undergoing this procedure, has not yet allowed a proper evaluation of a potential graft-versus-lymphoma effect.

Myelodysplastic syndrome
Allogeneic HSCT from a sibling donor is the treatment of choice for children with standard MDS, as well as secondary AML. As the possibility of cure is extremely poor with conventional chemotherapy, allogeneic HSCT from an unrelated donor can also be recommended. The role of autologous HSCT in children with MDS remains controversial.

Inherited diseases: primary immunodeficiencies
Primary immunodeficiencies are inherited disorders characterised by impairment of innate or adoptive immunity, commonly leading to lethal complications. Allogeneic HSCT can cure most of the lethal forms of immunodeficiencies, including: severe combined immunodeficiencies (SCID); several T-cell immunodeficiencies; Wiskott–Aldrich syndrome; phagocyte disorders such as leukocyte adhesion deficiency and chronic granulomatous diseases; haemophagocytic syndromes such as familial lymphohistiocytosis; Chediak–Higashi syndrome, Griscelli's disease; and X-linked lymphoproliferative syndrome. Treatment by HSCT is increasingly successful as shown by a recently published report from the SCETIDE (Stem Cell Transplantation for Immunodeficiencies) registry, established for the EBMT and the European Society for Immunodeficiency (ESID). Owing to the clinical heterogeneity of the patients, the several existing variants for each primary immunodeficiency associated with the need to carefully evaluate the patient's clinical conditions and the fact that drugs are utilized in different dosages, combinations and time schedules according to the disease, the age and the clinical condition of the patient, HSCT for primary immunodeficiency should be performed in a centre regularly performing such transplants and actively participates within EBMT's inherited diseases working party. The guidelines for each particular inherited condition are published on the EBMT's website and reviewed annually by the inherited disease working party members. Allogeneic HSCT is indicated for severe primary immunodeficiencies from both HLA-identical and alternative donors.

SCID
A patient with SCID needs to be grafted as soon as possible. The treatment of choice is an allogeneic HSCT, which results in a survival rate of more than 90% when carried out shortly after birth. Prognostic factors are the age, the type of SCID (B(+) vs B(−)), the clinical state at the time of diagnosis, in particular the presence of a lung infection, and the degree of HLA histocompatibility. In the presence of an HLA-identical family donor (20–30% of SCID patients), HSCT can be performed without any conditioning regimen and its course is characterised by the remarkable rarity of acute and chronic GVHD without any prophylaxis and by the rapid development of the T-cell function post transplant. The restoration of the B-cell function nearly always occurs in patients with the B(+) form of SCID, but is absent in 40% of those with a B(−) form. In the absence of an HLA-identical family donor, HSCT from a partially HLA-compatible donor is proposed. In this respect, the use of a conditioning regimen has a positive effect on survival in the B(−) SCID group but not in the other SCID groups. HSCT from unrelated HLA-compatible donor and haploidentical HSCT from related donors (i.e. one of the two parents) are alternative options.

Inherited diseases: metabolic diseases
Most of the metabolic diseases are lysosomal storage diseases and rely on transfer of enzyme from donor-derived blood cells to the reticulo-endothelial system and solid organs. The success of the HSCT can be affected by the success of engraftment (secondary rejection is comparatively common), the enzyme levels of the donor, the degree of sustained donor chimerism obtained, and possibly by immune processes directed against the normal donor enzyme. In disease with CNS involvement, amelioration is dependent on replacement of microglial cells by cells of donor origin. This process is slow and the time taken to process abnormal storage material produces a delay between transplant and disease stabilisation. This can last up to 15 months, making it necessary to best guess how the quality of life will be 18 months on from the first consideration of HSCT (allowing for a donor search, work-up and conditioning).

Aplastic anaemia, pure red cell aplasia (Blackfan–Diamond) and Fanconi anaemia
An allogeneic HSCT with an HLA-identical family donor is the treatment of choice for children with acquired severe aplastic anaemia. A course of intensive immunosuppressive therapy (ATG and cyclosporine A) is indicated for patients who lack a compatible family donor. The search for an unrelated donor should be initiated while they receive the immunosuppressive therapy. For children who fail their first course of immunosuppression, if a well-matched unrelated donor is identified, the transplant or a second course of immunosuppression should be given, according to clinical status. Children with Blackfan–Diamond anaemia, who have a matched sibling should be transplanted if they do not respond to steroids or if they do not eventually become independent of these drugs as long-term administration is associated with the risk of severe side effects. Children with Fanconi anaemia shall be transplanted if they have a normal HLA-identical sibling donor. For patients who lack genetically HLA-identical donors, a transplant should be considered with a well-matched unrelated donor or with cord blood stem cells in the context of a clinical protocol.

Haemoglobinopathies
The outcome of HSCT for thalassaemia has progressively been improved with the identification of the Pesaro Classes of Risk and the development of new conditioning regimens and supportive therapies. Allogeneic HSCT from a healthy related sibling donor or a related cord blood represents the treatment of choice for young patients with homozygous thalassaemia. For patients who lack a sibling donor, the possibility of undergoing a transplant from a well-matched unrelated donor should be evaluated in clinical protocols. Extended haplotype matching seems to impact positively on prognosis after unrelated donor HSCT. Developments of conventional therapy have improved both the quality and the duration of life for patients with Sickle Cell Disease. For this reason, HSCT from an HLA-identical sibling is offered only to a subset of patients at high, life-threatening risk. The experience of well-matched unrelated donor HSCT for Sickle Cell Disease is still very limited, and additional studies are needed.

Solid tumours
Despite much research in this field, no single solid tumour can be regarded as a standard indication for autologous HSCT in children. The only exception might be neuroblastoma (stage 4 beyond the age of 1 year, or high-risk factors in lower stages) and high-risk Ewing's sarcoma where prospective, randomised studies have indicated a clear advantage. Autologous HSCT should be performed according to approved protocols. Children with solid tumours may benefit from autologous HSCT following high-dose chemotherapy in the following situations:

- Germ cell tumours: after a relapse or with progressive disease Soft tissue sarcoma: stage IV or after a non-resectable relapse
- Wilm's tumour: high-risk histology or relapse
- Osteogenic sarcoma: the value of HSCT is not yet clear
- Brain tumours: children with medulloblastoma and high-grade gliomas responsive to chemotherapy.

Generally, allogeneic HSCT cannot be recommended in children with solid tumours. Allogeneic HSCT may be undertaken, however, in the context of a clinical protocol in specialist centres.

Autoimmune disorders
Selected patients with poor prognostic juvenile idiopathic arthritis are currently considered for autologous HSCT that has been proven as effective in providing a prolonged drug-free remission in a significant percentage of patients. Other diseases can be considered as developmental. The dependency of high steroid doses and impaired growth could be an indication.

Allogeneic HSCT with reduced conditioning in children
For patients otherwise not treatable (e.g. severe infections, heavy burden of chemotherapy, second transplants), allogeneic HSCT with reduced or minimal conditioning may be carried out within prospective clinical protocols. Developmental protocols in particular indications (e.g. solid tumours) may be undertaken as pilot protocols in specialised centres.

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